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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

HUTSON, RICHARD G

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 04/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/677,574

Applicant(s)

YANG ET AL.

Examiner

Richard G Hutson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 February 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9,11,12,14,15,17,18,20,37-40,43-64 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9,11,12,14,15,17,18,20,37-40,43-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 September 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11. 6) ☐ Other: _____

DETAILED ACTION

Applicants amendment of the specification and claims 1-9, 11, 12, 14, 15, 17, 18 and 20 and the cancellation of claims 10, 13, 16, 19, 21-36 and 41-42 and the addition of claims 43-64, Paper No. 15, 9/23/2002, is acknowledged.

Claims 1-9, 11, 12, 14, 15, 17, 18, 20, 37-40, and 43-64 are still at issue and are present for examination.

Applicants' arguments filed on 9/23/2002, paper No. 15, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

Applicants filing of three IDS's, April 3, 2001, January 31, 2002 and April 19, 2002, is acknowledged. Each of these have been considered and a copy or the initialed 1449 from the April 19, 2002 is enclosed.

Drawings

The newly submitted drawings have been approved by the draftsman.

Claim Objections

Claims 45 and 46 are objected to because of the following informalities: Claims 45 and 46 are duplicates of claims 7 and 9, respectively.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection was stated in the previous office action as it applied to previous claim 5 and its recitation "... mutants, variants, fragments and derivatives thereof."

In response to this rejection applicants have amended claim 5, such that it is now drawn to "... mutants and fragments thereof."

Applicants argue that the metes and bounds of mutants and fragments of said polymerases are clearly discernible to those skilled in the art in light of the functional and structural limitations of the polymerases set forth in claims 1 and 2. as well as the teachings at pages 21-25 and 36-53 of the specification. This argument is not found persuasive.

The rejection remains for the reasons previously stated. When does one DNA polymerase cease to be a mutant of one DNA polymerase and become a mutant of a different DNA polymerase? Expansion of this argument raises the issue that it is

unclear which, if not all known DNA polymerases, would be considered a mutant of the polymerases listed in claim 5, such that claim 5 does not further limit claim 3.

Claim 5, 44, 50 and 63 are indefinite in that each of these claims are drawn to the polymerase of claims 3, 43, 48 or 62, which are drawn to the DNA polymerase of claim 1 or 47, which is drawn to a nucleic acid polymerase that has been specifically modified at a position corresponding to Arg 722, Lys 726 or both Arg 722 and Lys 726 of a *Thermotoga neopolitana* polymerase. Claims 5, 44, 50 and 63 appear to further limit the polymerase of claims 3, 43, 48 or 62, and hence claims 1 or 47, in that it is selected from a group of known DNA polymerases. Claims 5, 44, 50 and 63 are indefinite in that the listed DNA polymerases are not modified at an amino acid position corresponding to Arg 722, Lys 726 or both Arg 722 and Lys 726, and thus Claims 5, 44, 50 and 63 do not further limit claims (claims 1 and 47) from which they ultimately depend.

Claims 12, 14, 15, 17, 18, 20, 56, 57, 58, 59, 60, and 61 are indefinite in that the reference to "amino acid position R (Arg722)" or "amino acid position K (Lys726)" in these claims is confusing, as there is no antecedent basis for amino acid position R or K in the claims from which these claims depend. Applicants amendment of these claims has resulted in the removal of the reference "amino acid position R" and "amino acid position K" from the claims from which these claims previously depended.

Claim 11 and 55 are indefinite in the recitation of "the O-helix of said polymerase", as it is unclear what is considered the O-helix of said polymerase. While applicants may teach a number of such O-helices of a number of known polymerases, it is unclear what in addition to that region of the polymerase defined by SEQ ID NO: 1, would be considered to be encompassed by the O-helix of a specific polymerase. In response to this rejection which was previously made for claim 10, applicants cancelled claim 10, amended claim 11 and added new claim 55 and traverse the rejection that was previously applied to claim 10 as it now applies to claims 11 and 55.

Applicants argue the highly conserved O-helix defines the nucleotide binding domain of DNA polymerases and that while positions within the O-helix domain may vary from species to species, as exemplified at page 20, it is well within the skill of an ordinary artisan to deduce other equivalent regions of polymerase O-helix domains based on the disclosure of the specification. This argument is not found persuasive because while the ordinary artisan may be able to deduce other equivalent regions of polymerase O-helix domains based on the disclosure of the specification, it remains that the metes and bounds of those amino acid positions which are considered to be encompassed by "an O-helix of said polymerase" is unclear. The identification of other equivalent regions of polymerase O-helix domains does not clarify those amino acid positions considered to be encompassed by "an O-helix of said polymerase".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11, 12, 14, 15, 17, 18, 20, 37-40, 43, 45, 46, 47-62 and 64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection was stated in the previous office action as it applied to claims 1-10 and 37-40. In response to this office action applicants have amended and added new claims and traverse this rejection as it applies to the new claims.

The newly amended claims are directed to all possible nucleic acid polymerases which have been modified or mutated at a position corresponding to Arg 722, Lys 726 or both Arg 722 and Lys 726 of a *Thermotoga neopolitana* polymerase and kits comprising said modified polymerases.

Applicants submit that the specification clearly discloses structural regions of the O-helix domains for different DNA and RNA polymerases at page 20 and that the specification clearly teaches and exemplifies how to generate mutations of polymerases for enhanced fidelity, reduced 3'-5' and/or 5'-3' exonuclease activities and/or reduced discriminatory activity against dideoxynucleotides. Thus applicants conclude that based on this disclosure, Applicants were in possession of what is being claimed.

Applicants argument is not found persuasive because while applicants have disclosed the structural regions of the O-helix domain for a number of previously known DNA and RNA polymerases, and exemplified how to generate mutations of a Tne

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polymerase for enhanced fidelity, reduced 3'-5' and/or 5'-3' exonuclease activities and/or reduced discriminatory activity against dideoxynucleotides, applicants have not adequately described the genus of polymerase mutants comprising any polymerase which has been modified at a position corresponding to Arg 722, Lys 726 or both Arg 722 and Lys 726 of a *Thermotoga neopolitana* polymerase, which includes polymerase variants of any Pol I, Pol II or Pol III-type DNA polymerases as well as reverse transcriptases and telomerases. The skilled artisan may not be able to determine those amino acid residues which correspond to Arg 722 or Lys 726 for many of the modified polymerases of the claimed genus, much less be able to modify these amino acids such that the modification results in the desired activity. There is no disclosure of any particular structure to function/activity relationship for the claimed genus. Given the lack of species representative of the claimed genus, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7, 11, 12, 14, 15,17, 46-49, 52 53, 55-59 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Astatke et al. (Journal of Biological Chemistry, Vol 270, No. 4, pages 1945-1954, 1995, ref AT, IDS, April 3, 2001).

Astatke et al. teach a number of site-directed mutants to identify those amino acids that interact with the deoxynucleoside triphosphate (dNTP) and pyrophosphate in the Klenow fragment-DNA-dNTP ternary complex, including DNA polymerase I R754A and K758A which correspond to R722A and K726A of *Thermotoga neopolitana* polymerase. While it is admitted that Astatke et al. do not teach the taught DNA polymerase I mutant has increased or enhanced fidelity or a reduced misincorporation of nucleotides during nucleic acid synthesis, however, these are considered to be inherent properties of the taught DNA polymerase I mutants.

Thus, claims 1-4, 7, 11, 12, 14, 15,17, 46-49, 52 53, 55-59 and 64 are anticipated by Astatke et al.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

A handwritten signature in black ink, appearing to read 'Richard G. Hutson', with a long horizontal line extending to the right.

Richard Hutson, Ph.D.
Primary Patent Examiner
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April 29, 2003